The Examiner stated that he understood that if rodents were not experiencing compromised reproductive success, then other mammals would not be experiencing adverse reproductive/health effects. However, the Examiner indicated that it was not clear that, if rodents were experiencing compromised reproductive success, the results could be extrapolated to make a determination as to the effects on other mammals.

II. SUPPLEMENTAL REMARKS

In view of the Examiner's comment at the interview, Applicant supplements the comments from the Amendment and Declaration filed on May 6, 2008.

1. It is standard for terrestrial ecological risk assessments, which are desktop exercises almost without exception, to assume that whatever health effects are anticipated or shown to develop in the mammalian test species (almost exclusively small rodents), will develop in the larger receptor species (mammals).

2. This extrapolation is seen first and foremost in the routinely-applied Hazard Quotient (HQ) calculation. See paragraphs [0005]-[0012] of the specification for discussion of HQs and their limitations in ecological risk assessment. In particular, desktop HQs (1) do not measure actual effects in the field, in contrast to the claimed field-truthing method which assesses multigenerational environmental stressors, and (2) do not teach the claimed benchmarks or thresholds-for-effect (paragraph [0010]).

3. When using a mouse or a rat no-effect dose or effect-level dose as the denominator of the HQ, it is asserted that other mammals are capable of, and do, develop the same toxicological effects as do the test rodents. Of note, this is routinely done where there has been no testing for other mammalian species.

4. All other site mammals have home ranges that are significantly greater than test rodent species, and consequently have significantly lesser degrees of exposure to contaminated media (e.g., soil, worms, plant matter). For HQ calculations, adjustments with regard to body weight, home range, and ingestion rate may be made. However, these affect only the magnitude of the resultant HQ. Making the adjustments has

nothing to do with the assumption that all site mammals will develop the same effect that the test rodents displayed. This assumption/extrapolation from the health effects in rodents to other mammals is routine and thus also applicable for the claimed methods.

5. Again, it is helpful to consider the standard scientific assumptions made in the *EPA Guidelines*, a document whose exclusive purpose is to apply rodent reproduction data to human assessment. According to the *EPA Guidelines,* "This notice describes the scientific basis for assessing potential risk to humans from exposure to environmental agents . . ." (page viii), and "These Guidelines describe the procedures that the EPA follows in using existing data to evaluate the potential toxicity of environmental agents to human male and female reproductive systems and to developing offspring." (page 1).

6. In the *EPA Guidelines*, please note the following:

A. (page 2) "An agent that produces an adverse reproductive effect in experimental animal studies is assumed to pose a potential reproductive threat to humans."

B. (page 2) "Because similar mechanisms can be identified in the male and female of many mammalian species, effects of xenobiotics on male and female reproductive processes are assumed to be similar across species unless demonstrated otherwise." (Emphasis added).

C. (page 2) "When sufficient data are available . . . to allow a decision, the most appropriate species should be used to estimate human risk. In the absence of such data, it is assumed that the most sensitive species is most appropriate because, for the majority of agents known to cause human reproductive toxicity, humans appear to be as or more sensitive than the most sensitive animal species tested."

7. Accordingly, as discussed at the interview, the present invention is conservative when sperm parameter exceedances in contaminated site rodents are extrapolated to make a determination about the health of or risk to larger mammals.

This is wholly consistent with current approaches (such as HQs and the *EPA Guidelines*) in extrapolating rodent data to other mammals.

8. This conservative extrapolation also makes sense because, other than for rodents, no one knows how much exposure (e.g., in terms of time) is required to trigger compromised sperm parameters in any species, including humans. Thus, for the claimed situation in which sperm parameter benchmarks are exceeded, it is correct to assume that the requisite exposures to trigger sperm and other reproductive effects in site mammals are occurring.

III. CONCLUSION

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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